# Positive Predictive Value of D-dimer in Diagnosing Pulmonary Embolism in Patients With No Risk Factors

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## Abstract

Serum D-dimer measurement is the most common screening test used to diagnose venothromboembolic disorders that constitute pulmonary embolism (PE) and deep venous thrombosis (DVT). D-dimer testing has high sensitivity but poor specificity to detect venous thromboembolism (VTE). Therefore, D-dimer testing for VTE is associated with high false positives.

Based on an elevated D-dimer, vast numbers of patients who have no risk factors are routinely worked up for PE with a battery of tests, including computed tomographic angiography (CTA) of the chest which exposes patients to significant radiation. We are not certain whether this elaborate workup is warranted in this subset of population with no risk factors. To address this concern, it was felt that knowing positive predictive value (PPV) of D-dimer in predicting PE in patients with no risk factors would be helpful. However, to our knowledge, no studies were documented in the literature assessing PPV in those with no risk factors for PE. Hence this study was designed.

**Objective:** To assess the PPV of Liatest D-dimer assay used at Druid City Hospital (DCH), Tuscaloosa, Alabama, in diagnosing PE among patients who have no risk factors based on revised Geneva score.

**Methods:** A retrospective chart review of family medicine patients with an elevated D-dimer seen from January 1, 2010, to December 31, 2010, at DCH, Tuscaloosa, Alabama, was performed. Based on revised Geneva score, patients without any risk factors were identified. Prevalence of PE in this subset of the population was calculated.

**Results:** There were 170 patient encounters with elevated D-dimer during the study period. Among those, based on revised Geneva score, 19 patients had zero risk factors and none of them had PE.

We recommend future studies to explore this more in depth. If future studies confirm this study's findings, new strategies may have to be implemented regarding the approach of PE workup in this subset of population with no risk factors.

## Introduction

Serum D-dimer measurement is the most common screening test used to diagnose venothromboembolic disorders that constitute pulmonary embolism (PE) and deep venous thrombosis (DVT). Plasma D-dimers are cross-linked fibrin derivatives produced when fibrin is degraded by plasmin. In general, D-dimer testing has high sensitivity but poor specificity to detect venous thromboembolism (VTE) as D-dimer can be elevated in any condition that causes activation of coagulation pathways, such as pregnancy, severe infection, liver disease, surgery, trauma, malignancy, ischemic heart disease, stroke, peripheral arterial disease, and advanced age.[1] As a result, D-dimer testing for VTE is associated with high false positives.

It is not uncommon for physicians to encounter patients with virtually no risk factors for PE and who may not have needed to have a D-dimer test done in the first place but ended up having one and it is elevated. In such scenarios, although it is known that D-dimer is associated with high false positives, physicians often find themselves obligated to perform an extensive work up to rule out PE because of concerns of medico-legal issues. Given the high occurrences of such situations, routinely based on an elevated D-dimer, vast numbers of patients with no risk factors are being worked up for PE. The work up often involves a battery of investigations including computed tomographic angiography (CTA) of the chest, an invasive test that exposes the patients to a significant amount of radiation. We are not certain whether this elaborate workup is warranted in this subset of population with no risk factors.

With this background, it was felt that knowing positive predictive value (PPV) of D-dimer in predicting PE in patients with no risk factors would be helpful. However, to our knowledge, no studies were documented in the literature assessing PPV in those with no risk factors for PE. Hence this study was designed.

## Objective

The objective of this study was to assess the positive predictive value of Liatest D-dimer assay used at Druid City Hospital (DCH), Tuscaloosa, AL, in diagnosing PE among patients who have no risk factors based on revised Geneva score.

## Methods

A retrospective chart review of family medicine patients with an elevated D-dimer seen from January 1, 2010, to December 31, 2010, at DCH, Tuscaloosa, AL, was performed. Exclusion criteria included patients younger than 18 years old and pregnant women. Of the patients who had an elevated D-dimer using revised Geneva score, patients with no risk factors for PE were identified. While both Wells criteria and revised Geneva Score are commonly used to employ the pre-test probability, we found it is more practical to use revised Geneva score since one of the criteria of Wells criteria is "alternative diagnosis is less likely than PE" which we feel is very subjective. Therefore, we preferred revised Geneva score. The risk factors used in revised Geneva score are age 65 years or over, previous DVT or PE, surgery or fracture within one month, active malignant condition, unilateral lower limb pain, haemoptysis, heart rate 75 or more beats per minute, pain on deep palpation of lower limb, and unilateral edema.[2] Prevalence of PE was calculated among these patients without any risk factors. PE was ruled out with CTA of the chest or ventilation-perfusion (V/Q) scan. In patients who did not have either of them, we ruled out PE based on three-month follow up.

Table 1 shows the parameters used in revised Geneva score. SAS version 9.2 was used for data analysis.

**Table 1**: Revised Geneva score

| |
|---|
| Age 65 years or over |
| Previous DVT or PE |
| Surgery or fracture within one month |
| Active malignant condition |
| Unilateral lower limb pain |
| Haemoptysis |
| Heart rate 75 to 94 beats per minute |
| Heart rate 95 or more beats per minute |
| Pain on deep palpation of lower limb and unilateral edema |

## D-dimer Assay

D-dimer levels are determined by Liatest assay at DCH, Tuscaloosa. It is an automated quantitative immunoturbidimetric assay. The assay is performed with the use of Diagnostica Stago kits. Based on normal-range studies performed across our health system, the Department of Pathology at our institution established a value of 420 ng/mL as the cutoff for venous thromboembolism. This standard cutoff value for the D-dimer assay is lower than that suggested by the manufacturer (500 ng/mL). Results were reported from the laboratory within approximately 20 minutes.

The study was approved by the Institutional Review Boards of both University of Alabama and DCH, Tuscaloosa.

## Results

There were a total of 170 patient encounters with elevated D-dimer during the study period. The mean age was 58.5 years. Females composed 76.4% of patient encounters. Of these patients, 55.3% were African American and the rest were Caucasian.

Of these patients, 19 qualified to have zero risk factors based on revised Geneva score. Of the patients with zero risk factors, 63.2% were female, 89.5% were African-American, and 10.5% were Caucasian. The median heart rate was 72 beats per minute. The median age was 53 years (range: 23-62 years) and none had PE. Table 2 shows the description of these patients.

**Table 2**: Description of patients without any risk factors based on revised Geneva score

| | |
|---|---|
| N | 19 |
| Gender | Females: 12 (63.2%) |
| Median Age | 53 (Range: 23-62) |
| Race | African American: 17 (89.5%)<br>Caucasians: 2 (10.5%) |
| Median Heart Rate | 72 beats per minute |
| D-dimer | 0.83 (0.43-2.29) |
| PE | 0 |

## Discussion

Since D-dimer was introduced as a screening test for VTE, it has been widely used because of its high negative predictive value, ease of administration, and short time for reporting results. These advantages have masked the fact that it has a very low positive predictive value. Because of its very low PPV and its wide usage, large numbers of false positives occur.

The increased number of false positives has resulted in excessive workup of PE with a battery of investigations including chest CTA. Although pulmonary angiography is currently the gold standard to diagnose PE, chest CTA is commonly used to diagnose PE. The current literature shows that chest CTA involves an effective radiation dose of 3 - 5 mSv, which is equivalent to one to two years of background radiation exposure. The lifetime attributable risk of lung cancer from this exposure can be anywhere from 38 to 118 cases per 100,000 patients depending on age and gender. The risk of breast cancer is also not negligible, especially in young women who have a risk as high as 503 per 100,000 excess cases.[3] In addition to radiation hazards, contrast-induced nephropathy occurs in 6.5% to 19% of patients who undergo chest CTA.[4]

The fact that most of those who were subjected to CTA based merely on an elevated D-dimer were not having PE prompted some authors to recommend usage of CTA based on clinical risk stratification and not solely based on an elevated D-dimer.[5,6]

Chopra et al[6] have assessed the diagnostic and financial yield of D-dimer in diagnosing PE. It is noteworthy that the PPV of 4.2% reported by Chopra et al is for all patients who had an elevated D-dimer and no value was mentioned based on clinical stratification. The authors also mentioned that "tests ordered based on elevated D-dimer values were billed for more than $200,000." Based on this, the authors concluded that "the current diagnostic approach has been medically and financially inefficient. Patients should not be worked-up for a PE based primarily on an elevated D-dimer value. Two prominent factors, independent of PE, that result in elevated D-dimer values and were pertinent to the studied population, are age and African-American origin. Implementing a scoring system, like the revised-Geneva scale, will establish a better index of suspicion to improve both the physician's diagnostic approach and the yield of the work-up."

Along the same lines, Deonarine et al[5] recommended that a "clinical probability assessment and d-dimer value should be combined and used to quantify the patient's risk of PE as low, moderate, or high. CTPAs are only indicated for those patients judged to be at moderate or high risk." The authors explain, however, that "this approach is seldom used in practice, resulting in unnecessary CTPAs being performed. This is an inefficient use of limited time and resources and exposes patients to avoidable irradiation and potential complications of iodinated contrast. Further research is required to better understand the challenges in promoting and implementing the routine use of clinical risk stratification for ambulatory patients with suspected PE."

Despite these recommendations, in reality it has become difficult to stratify elevated D-dimer patients on the basis of risk factors and use CTA accordingly, the most common reason for this being liability. Often, physicians feel that they are obligated to workup for PE in those who had an elevated D-dimer, regardless of patient's risk factors. We wonder if such a workup for PE, based merely on an elevated D-dimer is warranted; especially knowing that D-dimer can be elevated in several other conditions.

It was felt that knowing the PPV of D-dimer in predicting PE in patients with no risk factors could help us answer this question. Although there were few studies which assessed the overall PPV of D-dimer across all risk groups and also in low risk groups,[1,6] there were no studies documented in the literature studying PPV of D-dimer in those with no risk factors for PE. Our study suggested that positive predictive value of D-dimer in patients without any risk factors for PE was zero based on revised Geneva score.

Our study has two main limitations: the sample size was small and our study population may not represent the patient population generally seen in the emergency room (ER). Given the suggested low PPV of D-dimer in patients who do not have any risk factors, we recommend that adequately powered studies that represent the actual population of the ER are carried out.

The advantages of such studies are twofold: 1) If the value is found to be zero as evidenced by our study based on revised Geneva score, then we could defer doing any PE workup in those who have no risk factors, even if the D-dimer is elevated. This would be very appropriate if liability was the only reason for further workup. 2) We also believe it would be helpful to know the PPV of D-dimer in that subset of the population with no risk factors as it would help us in involving the patient in decision-making. In other words, if we come across a patient with no risk factors and an elevated D-dimer test, we can discuss with our patient the probability of having a positive CTA and the potential hazards of having a CTA. Based on this, our patients would be able to guide us in making a decision; some of them could choose to opt out of further workup if PPV is very low. This approach could again be beneficial in those scenarios where physicians think liability could be an issue.

In conclusion, we reiterate that our study suggested that the PPV of D-dimer in predicting PE in patients without any risk factors could be as low as zero. We recommend future studies to explore this more in depth. If future studies confirm this study's findings, new strategies may have to be implemented regarding the approach of PE workup in this subset of population with no risk factors in order to avoid the wasteful usage of resources and to prevent patients from getting unnecessary radiation exposure with CTA and putting them at risk of developing cancer.

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